Remarks

I. Addressing the Examiner's Rejections

A. Rejection of Claims 1, 8-10, and 12 Under 35 U.S.C. §102(b)

The Examiner rejected claims 1, 8-10, and 12 under 35 U.S.C. §102(b) asserting that the claims are anticipated by Dionne, et al., U.S. Patent No. 6,132,420.

For prior art to anticipate under 35 U.S.C. §102 it has to meet every element of the claimed invention: such a determination is one of fact. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986).

Federal Circuit decisions repeatedly emphasize that anticipation can be established only if all the elements of a claimed invention are identically set forth in a single prior art reference. The test is strict, not substantial, identity. *See, e.g., Transclean Corp. v. Bridgewood Services, Inc.*, 290 F.3d 1364, 62 USPQ2d 1865 (Fed. Cir. 2002); *Sandt Technology, Ltd. V. Resco Metal and Plastics Corp.*, 264 F.3d 1344, 60 USPQ2d 1091 (Fed. Cir. 2001).

Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 221 USPQ 481, 485 (Fed. Cir. 1984).

In view of the amendments to the claims presented in this response, the reference cited by the Examiner does not anticipate the presently claimed invention. All of the independent claims (*i.e.*, pending claims 1 and 15 and currently withdrawn claim 16) are amended to include the limitation that the semipermeable material of the preloaded membrane is saturated with the organic liquid filler material. The Dionne, et al., reference does not teach this limitation of the independent claims.

Dependent claim 12 distinguishes over the cited prior art at least by virtue of its incorporation of the limitations of independent claim 1. Claims 8-10 are canceled by this amendment.

In view of the amendment of the claims and the above-arguments, Applicants submit that the cited reference does not teach all the elements of the present invention. Accordingly, Applicants respectfully request withdrawal of the rejection of the claims under 35 U.S.C. §102(b).

B. Rejection of Claims 3-7, 11, and 13-15 Under 35 U.S.C. §103(a)

The Examiner rejected claims 3-7, 11, and 13-15 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Dionne, et al., U.S. Patent No. 6,132,420.

In *KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 82 USPQ2D 1385 (U.S. 2007), the Supreme Court reaffirmed use of the Graham factors in the determination of obviousness under 35 U.S.C. §103(a). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Supreme Court are as follows:

> (1) Determining the scope and content of the prior art;
> (2) Ascertaining the differences between the claimed invention and the prior art; and
> (3) Resolving the level of ordinary skill in the pertinent art. (*See Graham v. John Deere Co.*, 86 S.Ct. 684, 148 USPQ 459, 467 (U.S. 1966).)

Further, objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. *See Graham v. John Deere Co.*, 86 S.Ct. 684, 148 USPQ 459, 467 (U.S. 1966). Such evidence, sometimes referred to as "secondary considerations," may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. The evidence may be included in the specification as filed, accompany the application on filing, or be provided in a timely manner at some other point during the prosecution. *See* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57,526, 57,528 (October 10, 2007); Examination Guidelines Update: Developments in the Obviousness Inquiry After *KSR v. Teleflex,* 75 Fed. Reg. 53643, 53644 (September 1, 2010).

Independent claims 1 and 15 are pending, and independent claim 16 is currently withdrawn from prosecution. The dependent claims distinguish over the cited art at least by virtue of their incorporation of the limitations of the independent claims from which they depend.

1. The scope of the claimed invention and content of the prior art

The cited references do not teach all of the elements of the independent claims (as

presented in the accompanying amended claim set). Independent claims 1 and 15 contain the limitation that "the semipermeable material of the preloaded membrane is saturated with the organic liquid filler material." Withdrawn independent claim 16 contains a similar limitation. The Dionne, et al., reference does not teach or suggest this element of the independent claims. The Dionne, et al., reference teaches the addition of fluid additives (including polyethylene glycol (PEG) 400 and PEG 1000, propylene glycol (PG), polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan monooleate (Tween 80), dimethyl sulfoxide (DMSO), perfluorodecalin, silicone oils, organic liquids, and water or saline; *see, e.g.,* Dionne, et al., col. 6, lines 39-48) to the space surrounding osmotic tablets within a chamber of the osmotic device. The chamber is adjacent a membrane plug comprising a semipermeable material (*see, e.g.,* Dionne, et al., col. 4, lines 9-27). However, the reference of Dionne, et al., does not teach or suggest saturating the semipermeable material of the membrane plug with an organic liquid filler. Thus, the cited reference does not teach the claimed preloaded membrane comprising a semipermeable material and an organic liquid filler material contained within the semipermeable material, wherein the semipermeable material of the preloaded membrane is saturated with the organic liquid filler material.

Accordingly, a case of *prima facie* obviousness cannot be established.

2. The differences between the claimed invention and the prior art

"Ascertaining the differences between the claimed invention and the prior art requires interpreting the claim language, see MPEP §2111, and considering both the invention and the prior art as a whole." *See* MPEP §2141.

The reference of Dionne, et al., teaches the addition of fluid additives into the chamber of an osmotic device containing osmotic tablets to solve two problems associated with use of the tablets. The first problem is the presence of air spaces around the osmotic tablets that cause start-up delay for beneficial agent delivery from osmotic delivery systems. As discussed in the Background of the reference:

> Due to machining and tableting tolerances, the osmotic tablet in the solid initial state is generally sized somewhat smaller than the reservoir in which it is received. Thus, there are air-filled gaps between the osmotic tablet and the surrounding walls of the chamber, between the osmotic tablet and the

> membrane plug through which water is absorbed, and between the osmotic tablet and the piston. Due to these air-filled gaps, when water begins to be drawn into the osmotic tablet though the membrane plug, the osmotic tablet expands into the surrounding air space and beneficial agent delivery start-up is delayed by a time during which the osmotic tablet expands to fill the air spaces within the chamber. The start-up may be delayed up to several days or weeks depending on the size of the air gaps and the flow rate of the system. Delayed start-up of beneficial agent delivery is a significant problem in osmotic delivery systems. (Dionne, et al., col. 2, lines 3-18.)

The second problem is freezing-up or locking of the osmotic tablet against the sides of the chamber. As discussed in the Background of the reference:

> Another potential problem with known osmotic delivery systems is freezing-up or locking of the osmotic tablet against the sides of the chamber. The osmotic tablet passes through several states from the solid initial state to the hydrated delivery state. As the tablet begins to swell upon wetting it acts more like a solid than a deformable gel. Upon initial wetting, the swelling of the tablet can cause it to lock against the rigid capsule reservoir side walls causing the agent delivery to be delayed until sufficient water has permeated into the osmotic tablet to soften the tablet to the point where it flows. The freeze-up of the osmotic tablet upon initial wetting leads to delayed delivery. In addition, freeze-up can also lead to catastrophic problems such as membrane rupture, expulsion of the membrane plug, or a sudden increase in the delivery rate of the beneficial agent. (Dionne, et al., col. 2, lines 19-35.)

Neither of these problems relates to the semipermeable material of the membrane plug described in the Dionne, et al., reference. The reference contains no teaching concerning preloading a membrane comprising a semipermeable material with an organic liquid filler material, wherein preloading the membrane comprises saturating the semipermeable material of the membrane with the organic liquid filler material. Mere contact of a limited amount of an organic liquid filler material (such as PEG), contained in the osmotic agent chamber of an osmotic device, with a surface of a membrane plug comprising semipermeable material does not teach or suggest preloading and saturation of the semipermeable material by the organic filler material.

In the Office action, mailed 27 April 2010, the Examiner purports the following:

> With regards to the saturation of the preloaded membrane, the '420 patent discloses that capsule may contain only an osmotic agent in which case the osmotic agent would be present at a saturated level. (Office action, mailed 27 April 2010, page 5.)

It is unclear why the Examiner is referring to saturation of the "osmotic agent." However, as discussed above, the Dionne, et al., reference only teaches liquid filler added to the space surrounding osmotic tablets within a chamber of the osmotic device. The reference does not teach preloading and saturation of the semipermeable membrane with an organic liquid filler material.

Further, the Dionne, et al., reference was discussed in the Background of the present application as follows:

> In order to reduce the start-up time required by osmotic pumps, ALZA Corporation developed the device and methods described in U.S. Pat. No. 6,132,420 ("the '420 patent"). Though the technology described in the '420 patent provides a reduction in start-up time, the average start-up time exhibited by devices designed according to the teachings and methods of the '420 patent may still be inconveniently long in certain applications, and a device or method that provides an osmotic pump exhibiting an even further reduction in start-up time would be advantageous. Therefore, it would be an improvement in the art to provide an osmotic pump that both provides a further reduction in average start-up time and works to reduce the potential for a burst release of drug formulation as operation of the device commences. (Specification, ¶0006; emphasis added.)

The Examiner has not provided any evidence to support that one of ordinary skill in the art would have even tried saturating the semipermeable material of the membrane plug of an osmotic device to reduce average start-up time. The examiner bears the initial burden of establishing *prima facie* obviousness. *See In re Rijckaert,* 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). To support a *prima facie* conclusion of obviousness, the prior art must disclose or suggest all the limitations of the claimed invention. *See In re Lowry,* 32 F.3d 1579, 1582, 32 USPQ2d 1031, 1034 (Fed. Cir. 1994). In addition, the record must provide evidence that those of skill in the art would have had a reasonable expectation of success in doing so. *See In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). In the present case, the prior art does not disclose or suggest all the limitations of the claimed invention. Further, the record provides no evidence that would suggest a reasonable expectation of success (to achieve reduced average start-up time of osmotic delivery devices) using preloading of the membrane with an organic liquid filler, wherein the semipermeable material of the preloaded membrane is saturated with the organic

liquid filler material.

Regarding saturation of the semipermeable material, the present Specification teaches the following:

> A saturated, preloaded membrane according to the present invention includes a semipermeable material and an amount of liquid filler absorbed into the semipermeable material, with the amount of liquid filler absorbed into the semipermeable material resulting in a preloaded membrane that is unable to readily absorb additional amounts of the liquid filler. (Specification, ¶0025.)

As noted in the "Examination Guidelines Update: Developments in the Obviousness Inquiry After *KSR v. Teleflex,"* 75 Fed. Reg. 53643, 53644 (September 1, 2010) "[a]ny rationale employed must provide a link between the factual findings and the legal conclusion of obviousness." Here the Examiner has not presented any factual findings that teach or suggest preloading and saturation, with an organic liquid filler, of the semipermeable material of a membrane plug for use in an osmotic delivery device; in addition, the Examiner has not presented any reasoning or evidence to provide a link between the teachings of the Dionne, et al., reference regarding placement of a liquid filler into the space around the osmotic tablets in a chamber of the osmotic device and the presently claimed invention.

Applicants submit that the Examiner has not met the initial burden of establishing *prima facie* obviousness because all the limitations of the claimed invention are not taught by the cited reference and the record does not provide any evidence that one of skill in the art would have had a reasonable expectation of success achieving the claimed invention based on the teachings of the cited reference.

3. The level of ordinary skill in the pertinent art

In the Office action, mailed 27 April 2010, the Examiner did not address the level of skill of one of ordinary skill in the art. However, all the limitations of the claimed invention are not taught by the cited references and the record does not provide any evidence that one of skill in the art would have had a reasonable expectation of success achieving the claimed invention, as discussed herein above.

Accordingly, Applicants submit for the above-presented reasons that the Examiner has failed to establish a case of *prima facie* obviousness based on the cited references.

Applicants respectfully request that the rejections under 35 U.S.C. §103 be withdrawn.

4. Evaluation of objective evidence relevant to the issue of obviousness

Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. *See Graham v. John Deere Co.*, 86 S.Ct. 684, 148 USPQ 459, 467 (U.S. 1966). The present specification includes a great deal of objective evidence related to the problems solved by the present invention. As stated in the specification:

> In order to reduce the start-up time required by osmotic pumps, ALZA Corporation developed the device and methods described in U.S. Pat. No. 6,132,420 ("the '420 patent"). Though the technology described in the '420 patent provides a reduction in start-up time, the average start-up time exhibited by devices designed according to the teachings and methods of the '420 patent may still be inconveniently long in certain applications, and a device or method that provides an osmotic pump exhibiting an even further reduction in start-up time would be advantageous. Therefore, it would be an improvement in the art to provide an osmotic pump that both provides a further reduction in average start-up time and works to reduce the potential for a burst release of drug formulation as operation of the device commences. (Specification, ¶0006; emphasis added.)

Applicants made the unexpected discovery that a preloaded membrane saturated with organic liquid filler significantly reduced average start-up time, allowing osmotic pumps to reach target, or near target, drug delivery rates more quickly than osmotic pumps that do not include a preloaded membrane (*see, e.g.,* Specification, ¶0058). In fact, the present Specification provides a direct comparison between the osmotic devices of the Dionne, et al., reference and the osmotic devices of the present invention (*see,* Specification ¶¶0051-0059).

As described in the present Specification, to evaluate the benefits provided by the present invention, three groups of 16 osmotic delivery devices were manufactured and tested for release rate performance. Each of the osmotic delivery devices manufactured were loaded with a simulated drug formulation. In addition, each of the osmotic delivery devices was manufactured to provide a targeted drug formulation release rate of 0.35 ul/day for at least one year. To measure the release rate performance, each system was placed in a controlled temperature water bath maintained at 37°C, and the rate at which the simulated drug formulation was released from each system was measured (*see* Specification, ¶0051).

The first group of osmotic delivery devices was manufactured by, first, lightly

lubricating the piston and inner diameter of the reservoir using the silicon medical fluid. The piston was then inserted about 0.5 cm into the reservoir at the first end (hereinafter "the membrane end"). Two osmotic engine tablets (40 mg each) were then inserted into the reservoir from the membrane end. After insertion of the osmotic engine tablets, the resulting osmotic composition was flush with the membrane end of the reservoir. A semipermeable membrane plug was inserted into the reservoir by lining up the plug with the membrane end of the reservoir and pushing gently until the retaining features of the plug were fully engaged in the reservoir. The simulated drug formulation was loaded into a syringe, which was then used to fill the reservoir from the second end (hereinafter "the outlet end") by injecting the simulated drug formulation into the reservoir until the formulation was about 3 mm from the end. The filled reservoir was centrifuged (outlet end "up") to remove any air bubbles that were trapped in the simulated drug formulation during filling. The back diffusion regulating outlet was screwed into the outlet end of the reservoir until completely engaged. As the outlet was screwed in, excess amount of simulated drug formulation exited out of the delivery orifice, ensuring a uniform fill (*see* Specification, ¶0053).

The second group of 16 osmotic delivery devices are the devices taught by the Dionne, et al., reference. The devices were used as a control, and were manufactured using the same components and methods as were used to manufacture the first group of osmotic delivery devices, except that the second group of osmotic delivery devices was manufactured to include PEG 400 as a fluid filler distributed around the osmotic engine tablets that formed the osmotic composition. To accomplish this, 8 mg of PEG 400 was added through the membrane end of the reservoir after insertion of the piston. After the addition of the PEG 400, the two osmotic engine tablets were inserted into the reservoir through the membrane end, resulting in the PEG 400 substantially filling air gaps existing between tablets and the piston or the inner diameter of the reservoir. The piston, PEG 400, and osmotic engine tablets were added to each of the second group of osmotic delivery devices such that top of the osmotic composition formed by the osmotic engine tablets was flush with the first end of the reservoir. The membrane plug, the simulated drug composition, and the back diffusion-regulating outlet of each of the second group of osmotic delivery devices were provided as described for the first group (*see* Specification, ¶0054).

The third group of 16 osmotic delivery devices represented exemplary osmotic

delivery devices according to the present invention. These devices were manufactured using the same components and methods used to manufacture the second group of osmotic delivery devices, except that PEG 400 was preloaded into the membrane plug. PEG 400 was allowed to absorb into the membrane plugs included in each of the osmotic delivery devices of the third group under conditions that allowed saturation of the plugs by the PEG 400 (*see* Specification, ¶0055).

The average release rate performance exhibited by each of the three groups of 16 osmotic delivery devices is described in Table 1 (Specification, ¶0057) and illustrated in Figure 2 and Figure 3.

As is readily appreciated by reference to the table and figures, the osmotic delivery devices prepared according to the present invention provide a significantly reduced average start-up time, allowing the osmotic pump to reach target, or near target, drug delivery rates more quickly than osmotic delivery devices that do not include a preloaded membrane. Moreover, as can be seen in Table 2 (Specification, ¶0059), the average start-up time required by the third group of osmotic delivery devices was only 0.8% of the desired duration of drug delivery, while the average start-up time of the osmotic delivery devices of the second group represented 3.0% of the desired duration of drug delivery. Significantly, the osmotic delivery devices of the first group required more than 50 days to achieve steady state delivery of the simulated drug formulation and never achieved start-up (*see* Specification, ¶0058).

Applicants respectfully request the Examiner's careful consideration of these properties of the osmotic delivery devices of the present invention comprising a preloaded membrane comprising a semipermeable material and an organic liquid filler material contained within the semipermeable material, wherein the semipermeable material of the preloaded membrane is saturated with the organic liquid filler material.

II. Conclusion

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

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If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned at (650) 780-9030.

Respectfully submitted,

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